

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appl. No. : 10/806,829 Confirmation No.: 4240  
Applicant : Jian Bai, Steven M. Fischer and J. Michael Flanagan  
Filing Date : March 22, 2004  
Title : Ambient Pressure Matrix-Assisted Laser Desorption Ionization  
(MALDI) Apparatus and Method of Analysis  
Group Art Unit : 2881  
Examiner : Nikita Wells  
Docket No. : 10980322-4 (12089.4003)  
Customer No. : 022878

**DECLARATION OF STEVEN M. FISCHER PURSUANT TO 37 C.F.R. § 1.132**

MAIL STOP AMENDMENT FEE  
Commissioner of Patents  
P.O. Box 1450  
Washington, D.C. 20231

Sir:

1. My name is Steven M. Fischer. I am a named inventor of patent application serial number 10/806,829 entitled "Ambient Pressure Matrix-Assisted Laser Desorption Ionization (MALDI) Apparatus and Method of Analysis." This application generally describes the first implementation of matrix-assisted laser desorption ionization of analytes at ambient pressure, and describes the ability to perform MALDI on an analyte in solution without adding any matrix to the solution.

2. I received a Chemistry degree from California State Hayward University in 1981.

3. I am Senior Research and Development Chemist at Agilent Technologies Inc. where I have worked for 23 years. I have 17 years of experience in mass spectrometry and 12 years of specific experience in laser-induced ionization of analytes present in a matrix.

4. I have over forty patents related to LC/MS hardware, software and chemistry and approximately ten peer reviewed publications. In 1998, I was working extensively in the field of mass spectrometry and am familiar with the state of the art based on my own work and also from reading literature in the field, attending conferences, working with customers and other activities.

5. I have read U.S. patent 6,683,300 to Doroschenko and the patent claims that describe the use of matrix-assisted laser desorption/ionization of an analyte in solution without the use of an added matrix. I have also read the Office Action from the United States Patent Office sent February 25, 2009. I have considered whether or not one skilled in the art of chromatography and mass spectrometry in 1998 would determine from the content of our patent specification that we possessed and described a method of performing MALDI on an analyte in a liquid solution without any added matrix.

6. Our patent application describes the development of new ionization techniques and ion sources for mass spectrometry that work with flowing chromatographic systems such as HPLC, LC or GC. The development of ion sources that are compatible with chromatography result in more useful analytical techniques. Electron Impact (EI) and Chemical Ionization (CI) ion sources are successful GCMS sources because they easily interface to GC. We successfully demonstrated that AP-MALDI would work with water and a Infrared (IR) laser and that the ion source could be used with an HPLC or CE. We describe this in our application at pages 10-11 of our application where we describe the direct connection between these chromatography apparatus and a mass spectrometer. Water is the most common solvent used in HPLC, and

successfully making ions from water would mean that flow MALDI could be performed on HPLC separations using water without the addition of anything else. This capability is described in detail in our application where the laser energy applied directly to the analyte in solution. See pages 10-12. All of these techniques and capabilities would demonstrate to one skilled in the art that MALDI could be performed directly on the analyte in solution without added matrix.

7. Our application also says in plain text of the document to use a laser to irradiate a liquid analyte solution without an additional matrix for at least the following reasons:

a) The “matrix” described in our application is any substance that absorbs a photon and subsequently transfers charge to an analyte. We describe performing MALDI directly on a liquid solution by directing the laser to the effluent from a chromatography apparatus. The specification states:

“Flowing” refers to a liquid sample or matrix which is moving and from which the sample and matrix is analyzed.

“Holder” also refers to an interface for introducing a moving liquid e.g. the effluent from a HPLC or CE a syringe pump and the like.

See application at page 10.

b) the application discloses the ability to perform MALDI on an analyte in a water-based solution using IR (infrared laser). This description is in the context of a chromatographic system where the laser is directed to the chromatographic effluent to ionize the analyte in solution. Water is the most common solvent for chromatography and we specifically describe using water as the matrix element without any additional matrix. The portions of our application that describe this are as follows:

“Matrix” refers to any solid or liquid molecules having the ability to transfer or receive a charge from the analyte and an absorption of the wave length of the laser ....

\* \* \*

For an infrared laser, aliphatic organic compounds, hydrocarbons, aliphatic organic compounds which contain heteroatoms such as oxygen nitrogen, sulfur, and combinations thereof, water and combinations of these compounds which can transfer to or receive a charge from the analyte are suitable. Application page 11. (emphasis added)

\*\*\*

The analyte matrix may be a liquid such as water or alcohol e.g. methanol, or a solid such as ice.

Application page 13.

c) consistent with ordinary usage, the application defines the matrix as performing the function of absorbing laser energy and transforming the charge to the analyte. In our application, the liquid containing the analyte acts as the matrix and no additional matrix is used. The absence of additional matrix is clearly shown in the application where we describe the use of the solvent as the matrix and instruct the use of a laser that is appropriate to the solvent. In other words, we specifically teach to match the solvent to the laser because the solvent acts as the matrix, for example, an IR laser is used for water, and a UV laser is used with acetone. The laser wavelength is based on the solvent because the solvent is acting as the matrix and no additional matrix is necessary or useful. The fact that we specifically tell the MALDI practitioner to match the laser with the analyte solution means that we are describing performing the MALDI technique on an analyte in liquid solution without added matrix. The application states:


"Matrix" refers to any solid or liquid molecules having the ability to transfer or receive a charge from the analyte and an absorption at the wavelength of the laser, such as ultraviolet (UV), (electronic), visible (VIS) or infrared (IR) (vibrational and/or rotational) or combinations thereof. For an ultraviolet laser,

substituted aromatic compounds are used which can transfer or receive a charge to or from the analyte. For an infrared laser, aliphatic organic compounds, hydrocarbons, aliphatic organic compounds which contain heteroatoms such as oxygen, nitrogen, sulfur, and combinations thereof, water and combinations of these compounds which can transfer to or receive a charge from the analyte are suitable.

Specification page 11.

8. I, the undersigned, being hereby warned that willful false statements made herein are punishable by fine or imprisonment or both under 18 U.S.C. 1001, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon, do hereby declare that all statements made herein of my own knowledge are true, and that all statements made on information and belief are believed to be true.

Date: 8/21/2009

By:   
Steven M. Fischer